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Systematic review on Rapid Diagnostic Tests for meningococcal meningitis disease in sub-Saharan Africa WHO Protocol to inform the revision of meningitis outbreak response guidelines

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BACKGROUND

For over 100 years, major epidemics of meningococcal disease have occurred every few years within the African meningitis belt (Lapeysonnie). These epidemics are very disruptive, requiring the establishment of emergency treatment centres and placing a severe strain on the routine health services. Most epidemics have been due to Neisseria meningitidis serogroup A (Nm A), with some earlier outbreaks caused by serogroup C, and more recently, serogroups W and X. Since 2010 countries in sub-Saharan Africa have started to progressively introduce a new meningococcal A conjugate vaccine (MenAfriVac) through mass campaigns as a preventive measure that is expected to confer both long lasting individual protection and herd immunity (Sow 2011, Novak 2012, Kristiansen 2012, Daugla 2013). The wide-scale introduction of MenAfriVac should result in the disappearance of significant Nm A epidemics, whilst outbreaks due to meningococci of other serogroups such as W, X and C are likely to continue. Nm W, in particular, has been responsible for several epidemics in the last ten years e.g. Burkina Faso, Niger, Ghana.

Rapid Diagnostic Tests (Index Tests)

Rapid diagnostic tests have been defined as any test that yields a result in the same clinic visit as diagnosis (Pai et al 2012) or which can be used in healthcare settings with little infrastructure or trained personnel, preferably without electricity (Yansouni et al 2013). For

rapid diagnosis of bacterial meningitis, immunochromatography or latex agglutination tests have been the techniques most commonly used.

For diagnosis of meningococcal meningitis, duplex dipsticks have been developed in order to enable identification of four different serogroups of N. *meningitidis*, A, C, W and Y using a cerebrospinal fluid (CSF) sample obtained by lumbar puncture. A similar technique has been developed for S. *pneumoniae.*

A duplex dipstick designed by the Centre de Recherche Médicale et Sanitaire (CERMES) (Niamey, Niger) and the Pasteur Institute National Reference Centre for Meningitis (Paris, France) was initially criticised for variation in results obtained in the field, which was put down to batch-to-batch performance variation in the serogroup A monoclonal antibody used (Chanteau 2006). A new conjugated antibody (L4-8) for the detection of serogroup A has now replaced the original (K15-2) antibody (Collard, unpublished paper).

The Alere BinaxNOW immunochromatographic test works on a similar principal to the CERMES/Pasteur N. Meningitides dipstick. It is an in vitro rapid immunochromatographic assay for the detection of S. *pneumoniae* antigen in the urine of patients with pneumonia and in the cerebral spinal fluid (CSF) of patients with meningitis. In conjunction with culture and other methods, it is intended to aid in the diagnosis of both pneumococcal pneumonia and pneumococcal meningitis.

Latex Agglutination Tests (LATs) are a widely used and valuable tool for rapid diagnosis of meningitis at the bedside, however they are relatively costly and require a cold chain for transport and storage, which is rarely practical in sub Saharan outbreak conditions. The Pastorex LAT (Djibo et al 2006) is available as a kit which consists of colored latex particles coated with mouse monoclonal or rabbit polyclonal antibodies for the direct qualitative detection and identification of Neisseria *meningitidis,* A, B/E *coli* K1, C, Y/W 135; Haemophilus *influenzae* Type b; Streptococcus *pneumoniae*; and group B *streptococci*.

This review is intended to provide guidance to support a WHO review of use of RDTs in field conditions in sub-Saharan Africa, as part of revised WHO guidelines for the management and response to outbreaks of meningitis in the region.

Clinical Pathway

Following patient presentation to hospital or clinic, if a diagnosis of bacterial meningitis is suspected, a lumbar puncture is undertaken. The CSF sample is tested at point of sampling with an RDT, when available, and the remaining sample sent for reference testing at a regional / national laboratory. Antibiotic treatment may be commenced at any point in this pathway, but ideally after the CSF sample has been obtained, as quickly as possible anyway. If RDT or reference test results are available at time of treatment, and they indicate *S. pneumoniae* or *H. influenzae*, antibiotic treatment will be continued for 5-7 days.

If RDT or reference test indicate N. *meningitidis* the patient is given a single dose of antibiotics. In general, laboratory results are not readily available at time of treatment and

case management is then based on presumptive treatment. In confirmed meningococcal epidemic situations single dose antibiotic treatment is used in patients over two years of age, while 5-7 day treatment is used in children 0-23 months. In non-epidemic situations, 5 to 7 day antibiotic treatment is used (exact treatment protocol depends on age of patient and most likely causative pathogen) (WHO 2007, 2010).

Role of index test

It is anticipated that the index test will inform use of the reference standard (CSF culture and/or PCR). Reference standard tests must take place at a distant laboratory which can delay accurate characterisation of disease by many days. The role of the index test is therefore to provide timely guidance to inform outbreak response or vaccination campaigns, as well as to provide bedside, rapid results for the individual.

Rationale for review

It is ever more critical to ensure that the causal pathogen in outbreaks of meningitis is confirmed rapidly, particularly since the epidemiological shift brought about by the introduction of the MenAfriVac for N. *meningitidis* serogroup A (NmA). In many instances, reactive vaccination may occur too late to effectively reduce the size of outbreaks and epidemic presumptive case management may be less appropriate. RDTs are useful to support urgent decision-making for outbreak management. However, latex agglutination tests e.g. Pastorex, are expensive, not easy to use and not always reliable. Immunochromatographic tests have not yet been widely deployed. A review of the sensitivity and specificity of different rapid diagnostic tests compared to the gold standard of culture or PCR is therefore needed. This systematic review, commissioned by the WHO, will summarise the diagnostic accuracy of RDTs, in turn supporting the development of revised WHO guidelines for outbreak response and management in sub-Saharan Africa.

OBJECTIVES

Aim

To identify rapid diagnostic tests for bacterial meningitis and determine the diagnostic accuracy (including the sensitivity and specificity) of each compared to the gold standard of culture or PCR.

Objectives

Process objective

1) To undertake a systematic review of the literature using agreed search strategies

Output objectives

2) To determine combined estimates of the sensitivity and specificity of each identified Rapid Diagnostic Test for distinguishing between serogroups of N. *meningitides.*
3) To determine combined estimates of the sensitivity and specificity of each identified Rapid Diagnostic Test for N. *meningitides.*
4) To determine combined estimates of the sensitivity and specificity of each identified Rapid Diagnostic Test for S. *pneumonia.*
5) To determine combined estimates of the sensitivity and specificity of each identified Rapid Diagnostic Test for *H. influenza*.

We will report test performance under laboratory and field conditions separately including reported differences in sensitivity and specificity between RDTs and reference tests, and different commercial brands of index tests. We will, if possible, assess the impact of disease prevalence and seasonality on the sensitivity and specificity of RDTs.

METHODS

Criteria for considering studies

Types of Studies

We will include diagnostic accuracy studies which assess the accuracy of RDTs in the laboratory or in field conditions, in which all patients are given both the index test and a reference standard. These studies may be cohort studies or randomised comparisons of tests in which patients are randomised to one of several index tests with all receiving the reference standard test.

Participants

Patients with suspected bacterial meningitis who have symptoms or signs of meningococcal disease according to WHO guidelines (WHO 1998) and successful lumbar puncture. We will exclude studies that examine only causative organisms other than N. *meningitidis*, S. *pneumoniae* or H. *influenzae*. In studies where only a particular subgroup is eligible for this review, we will include the study if it is possible to extract data relating specifically to that subgroup.

Index tests

All cerebrospinal fluid RDTs made by any manufacturer for bacterial meningitis which can be performed in field conditions.

Target conditions

The target condition is acute bacterial meningitis including N. *meningitidis*, S. *pneumoniae* and H. *influenzae*. In the case of N. *meningitidis*, the specific serogroup is to be identified by the index test.

Reference standards

In developing countries, the most commonly used approaches for detection and characterization of bacterial meningitis pathogens include culture, Gram stain, and latex agglutination. The gold standard of diagnosis of meningitis is culture and PCR of cerebrospinal fluid (CSF) although in field settings, the positive rate from culture is relatively low due to suboptimal storage and transportation conditions, culture practice, and/or antibiotic treatment administered before the specimen is collected (CDC 2012). For culture, CSF is drawn from suspected cases of meningitis by lumbar puncture and cultured on enriched media such as blood agar or chocolate agar. PCR detection of N. *meningitidis*, H. *influenzae*, and S. *pneumoniae* can be achieved by amplification of several potential gene targets (Carvalho et al 2007, Mothershed et al 2004, Taha et al 2005, Wang et al 2011). Organism specific assays have been developed and validated to be used on DNA extracted from clinical specimens (typically, blood and CSF) and bacterial isolates. The use of such techniques is limited to a small number of reference laboratories in sub-Saharan Africa, requiring transport for several days of samples stored at 4 or -20 degrees centigrade and is thus rarely useful for clinical decision-making.

Acceptable reference standards for diagnosing organisms responsible for acute bacterial meningitis include:

- Culture of blood or CSF
- Blood or CSF Polymerase Chain Reaction (PCR) (bacterial species and meningococcal serogroup) either simplex or multiplex

SEARCH METHODS

Electronic Searches

We will attempt to identify all relevant studies regardless of publication status, without language or publication date limit. Only studies conducted exclusively in humans will be considered. Experts from the WHO guideline development group will be consulted to identify research which may not yet be published.

We will search for systematic reviews using:

- The Cochrane Library (including DARE)

- Medline/Ovid
- EMBASE
- CAB/ Global Health
- TRIP

If a systematic review is identified, we will search for additional primary studies from the date of that review. Unless explicitly included in any systematic reviews, the search for primary studies will be extended using African Index Medicus, WHO Regional databases and grey literature using Google with country filters (eg. meningitis site:gov.nb). In the absence of a systematic review, the following electronic literature databases will be searched without publication date limit:

- Medline/Ovid
- EMBASE
- African Index Medicus
- Cochrane Library (CENTRAL)
- CAB/Global Health
- WHO Regional databases
- Grey literature, including:
    - Relevant commercial websites for identified RDTs
    - Google searches with country filters e.g. meningitis site:gov.nb

MeSH terms will include: bacterial meningitis, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, immunoassay, chromatography, immunochromatography, Latex Agglutination Test, Diagnostic test. Other search terms will include rapid diagnostic test*, RDT and dipstick*. Predetermined search terms for diagnostic accuracy studies from SIGN will be used, adapted from filters from the Health Information Research Unit of the McMaster University, Ontario. No language restriction will be used. Search terms are provided in detail at appendix 1.

In addition to this search strategy, the reference lists of the included reviews and papers will be checked. Experts in the field of meningococcal disease will be consulted to identify any additional sources of material. It is anticipated that the Guideline Development Group of the WHO will provide such expertise.

Study selection will be performed by two researchers independently in two phases: phase one will consist of screening titles then abstracts of identified studies. Full text will be reviewed in the absence of an abstract. Papers which clearly do not meet inclusion criteria will be excluded in this phase. In phase 2, the full text of remaining studies will be screened.

Data extracted will be entered in evidence tables using a template from the Belgian Healthcare Knowledge Centre (KCE) (see appendix 2). Any disagreements will be resolved by discussion or, if required, by a third party. Meta-analyses will be performed according to

the guidelines described in the (draft) Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks 2010).

DATA COLLECTION AND ANALYSIS

Data extraction and management

The data to be extracted for each paper included in the review is shown at appendix 3.

Assessment of methodological quality

Those papers selected for inclusion will be and appraised for quality, again by two researchers independently. Any disagreements will be resolved by discussion or with consultation of a third researcher in case of persisting disagreement. Content experts will be involved to judge any other flaws that could be overlooked by non-experts.

The quality of systematic reviews (if identified) will be assessed by the use of AMSTAR (Shea 2007). In order to label all 'yes' scores as 'low risk of bias' item 4 of AMSTAR will be reversed and rephrased as follows: "4. The status of publication (i.e. grey literature) should not have been used as an inclusion criterion. Was this the case?" For primary diagnostic test accuracy studies we will use QUADAS-2 (Whiting 2011).

Using the QUADAS 2 tool, both researchers will independently assess the quality of each paper. All questions will be answered as either 'yes', 'no' or 'unclear' with reasons documented according to the checklist illustrated at appendix 4.

Statistical Analysis and Data Synthesis

The extent and nature of statistical analysis to be undertaken will be heavily dependent on the number of papers found. Laboratory and field testing will be analysed separately, if sufficient data is available.

Rapid diagnostic tests can discriminate, amongst others, between the various bacterial species and between individual Neisseria *meningitidis* serogroups A, C, W, X or Y. Available vaccines are directed to Spn, Hib or Nm (A, AC, ACW or ACWY). We will therefore compare the results of the various rapid diagnostic tests with the reference standards and construct two-by-two tables for a correct choice of the vaccine to be used, based on the index test. Performance under laboratory and field conditions will be assessed, as will positive and negative predictive values.

Outcome data will be presented as 2x2 tables, extracted and summarised from the identified papers. Where only sensitivity and specificity estimates are reported without 2x2 tables, we will try to derive the 2x2 tables from those. For each study sensitivities and specificities will be presented as paired forest plots with 95% confidence intervals.

Both culture and PCR of CSF are considered to be reference standards for diagnosis of bacterial meningitis. If there is a split between papers which use PCR, culture or both then data on these reference tests, including sensitivity and specificity (if not 100%) will be presented separately.

If - as expected - a uniform threshold is applied for each index test across studies, pairs of sensitivity and specificity will be used to calculate a summary estimate of sensitivity and specificity using a generalized linear mixed model (binomial family) (Reitsma 2005). If thresholds vary across studies, then the underlying Receiver Operating Characteristics (ROC) curve will be estimated by the use of a Hierarchical Summary Receiver Operating Characteristics (HROC) model (Harbord 2007).

Investigations of heterogeneity

Commercial brands will be analysed separately in order to allow for heterogeneity between test kits. Furthermore, studies conducted under field conditions will be considered separately from those conducted under laboratory conditions. We will investigate heterogeneity by adding location and type of reference standard (eg culture vs PCR) as covariates to the model.

Assessment of reporting bias

There will be no formal assessment of reporting bias as no sound methods are available for diagnostic test accuracy studies.

ROLES AND RESPONSIBILITIES

TW – protocol design, develop study tools, literature searches, literature review, assess quality, data analysis, report write up

LS – assess study quality, literature review, report write up

MG – protocol design, oversee literature review and data analysis, manuscript preparation

OR – oversee systematic review process

KF – oversee systematic review process

JS – protocol design, oversee literature searches and review, oversee data analysis, report write up

RS – method expert, oversee literature searches and review, analysis design, report write up

TIMESCALES

September Protocol design, write up

October	Literature searches and review, amend protocol based on Cochrane input
November	Literature searches and review, commence data analysis
December	Data analysis, manuscript preparation
January	Manuscript preparation and review
February	Presentation to WHO guideline review group, review and submission of manuscript for peer review

OUTPUTS

A report of findings will be generated and presented to the WHO meningitis guideline development group and will be used to inform the WHO guideline development process. In addition, manuscripts will be prepared for publication in appropriate peer reviewed journals.

APPENDIX 1 – Specimen search terms

Search string	MEDLINE		EMBASE	
DISEASE OF INTEREST				
1	Exp meningitis	[MeSH]	exp meningitis/	[Emtree]
2	Exp Neisseria meningitidis	[MeSH]	exp bacterial meningitis/	[Emtree]
3	Exp Haemophilus influenzae	[MeSH]	Exp epidemic meningitis/	[Emtree]
4	Exp Streptococcus pneumoniae	[MeSH]	Exp meningococcosis/	[Emtree]
5	Exp meningococcal infections	[MeSH]	Exp Neisseria meningitidis/	[Emtree]
6	Exp pneumococcal infections	[MeSH]	Exp Streptococcus pneumoniae/	[Emtree]
7	Exp Haemophilus infections	[MeSH]	Exp Haemophilus influenzae/	[Emtree]
8	**Meningitis.tw. OR meningitidis.tw. OR meningococcal.tw. OR pneumococcal.tw. OR Haemophilus.tw.**		**Meningitis.tw. OR meningitidis.tw. OR meningococcal.tw. OR pneumococcal.tw. OR Haemophilus.tw.**	
9	1-8/or		1-8/or	
TESTS				
10	Exp Reagent kits, diagnostics	[MeSH]	Diagnostic test/	[Emtree]
11	Rapid diagnos* test*.tw		Rapid diagnos* test*.ti,ab	
12	RDT.tw		RDT.ti,ab	
13	Dipstick*.tw		Dipstick*.ti,ab	
14	Rapid diagnos* device* .tw		Rapid diagnos* device* ti,ab	
15	Binax NOW .tw		Binax NOW ti,ab	
16			**Pastorex**	
17	Immunochromatograph*.tw		Immunochromatograph*ti,ab	
18	Antigen detection method* .tw		Antigen detection method* ti,ab	
19	Antigen detection.mp.		Antigen detection/	[Emtree]
20	Antibody detection.mp.		Antibody detection/	[Emtree]

21	Latex fixation test	[MeSH]	Latex agglutination test/	[Emtree]
22	Agglutination test*.tw		Agglutination test*.tw	
23	Immunoassay	[MeSH]	Immunoassay/	[Emtree]
24	Chromatography	[MeSH]	Chromatography/	[Emtree]
25	Rapid test* .tw		Rapid test* .ti,ab	
26	Rapid AND (detection* or diagnos*) .tw		Rapid AND (detection* or diagnos*) .ti,ab	
27	10-26/or		10-26/or	
TEST ACCURACY				
28	exp "Sensitivity and Specificity"/	[MeSH]	exp "Sensitivity and Specificity"/	[Emtree]
29	Sensitivity.tw		Sensitivity.tw	
30	Specificity.tw		Specificity.tw	
31	((pre-test or pretest) adj probability).tw.		((pre-test or pretest_ adj probability).tw.	
32	Post-test probability.tw.		Post-test probability.tw.	
33	Predictive value*.tw.		Predictive value*.tw.	
34	Likelihood ratio*.tw		Likelihood ratio*.tw	
35	28-34/or		*Diagnostic Accuracy/	[Emtree]
36	9 and 27 and 35		27-34/or	
37	Limit 36 to human		9 and 27 and 35	
38	**n/a**		Limit 36 to human	
AFRICAN INDEX MEDICUS			**COCHRANE LIBRARY (CENTRAL) & Pubmed**	
1	Meningitis		Mening*	
2	Neisseria meningitidis		Neisseria meningitidis	
3	Haemophilus influenzae		Haemophilus influenzae	
4	Streptococcus pneumoniae		Streptococcus pneumoniae	
5	1-4/or		1-4/or	

6	Diagnosis		Diag*	
7	Diagnostic		Dipstick	
8	Dipstick		RDT	
9	RDT		Rapid diagnos* test*	
10	6-9/or		6-9/or	
11	5 and 10		5 and 10	

Appendix 2 – literature search data flow tables

Table 2.1 Data flow from literature search (use one for systematic reviews and one for primary study articles)

Number of articles identified	|__|__|__|__|
Number of duplicate articles	|__|__|__|__|
Number of total articles considered	|__|__|__|__|
Number of titles screened	|__|__|__|__|
Number of abstracts screened	|__|__|__|__|
Number of full texts screened with no abstracts	|__|__|__|__|
Total number of full texts screened (also complete table 1.2)	|__|__|__|__|
Total number of articles included in the study	|__|__|__|__|

Table 2.2 Full text screen of articles

Author	_____
Year of publication	|__|__|__|__|
Is article to be included in study (0=no; 1=yes)	|__|
If no reason	_____ _____
Study number (only allocate if article to be included in study)	|__|__|

Table 2.3 Evidence table for systematic review

Study ID	Method	Patient characteristics	RDT and reference test	Results	Critical appraisal of quality
|__|__|	_____	_____	_____	_____	_____
|__|__|	_____	_____	_____	_____	_____
|__|__|	_____	_____	_____	_____	_____
|__|__|	_____	_____	_____	_____	_____

Appendix 3 – data to be extracted for each paper included in review

Study name / date	Authors, publication date and number
Clinical features, setting	Diagnosis Setting of test (lab or field)
Participants	Sample size Characteristics if reported • Demography • Gender • HIV status • Country • Vaccine status
Study design	Sampling strategy Outbreak setting Number of RDTs evaluated Method of allocation of subjects each RDT (if applicable)
Target condition	• All bacterial meningitides • *N. meningitidis* / meningococcal serogroup • S. *pneumoniae* • *H. influenzae*
Reference standard	CSF culture PCR Culture and PCR PCR type Location of reference test Time between RDT and reference test Blinding of operator to RDT Was any subset subject to a different reference test? • Why? • How many? Details of storage and transport conditions / cold chain
Index test	Name – commercial name, batch number, antibody type Detection target Need for sample preparation Who did the test? Training provided to operator Location of test
Index and reference standard test results	Missing results for index and reference Uninterpretable results for index and reference Borderline results for index and reference True and false positives True and false negatives Sensitivity and specificity of index tests Repeat the above if more than one reference standard test used
Notes	Details of relevance

Appendix 4

Patient Selection	
Was a consecutive or random sample of patients enrolled?	"Yes" if this is well described in the paper (eg consecutive or a random sample from consecutive patients) "No" if the sample was non-random or patients were not consecutively recruited "Unclear" if there is insufficient information to make a judgement on the selection of patients
Was a case control design avoided?	Self explanatory
Did the study avoid inappropriate inclusions?	"Yes" if inclusion and exclusion criteria clearly described and appropriate "No" if inclusion and exclusion criteria clear but include inappropriate subjects, eg those with a known existing diagnosis "Unclear" if there is insufficient information to make a judgement on the inclusion of subjects
Could the selection of patients have introduced bias?	"Yes" if it is clear that bias is introduced through, for example, non-random selection "No" if the selection of patients is clearly described and does not introduce bias. "Unclear" if there is insufficient information to make a judgement on the impact of selection on bias
Are there concerns that included patients do not match the review question?	"Yes" if included patients are inherently different from the cohort of patients who would be expected to receive the RDT in sub-Saharan Africa (eg used as a laboratory check in a Western country) "No" if there are no such concerns "Unclear" if patient characteristics are not sufficiently clearly explained to make a judgement on this
Index Test	
Were the index test results interpreted without knowledge of the results of the reference standard?	"Yes" if the paper states that the index test is interpreted by individual(s) who did not know the results of the reference test(s) "No" if the results of the index test were known by the individuals performing the reference test, or if the same individual performed both tests Unclear if…
If a threshold was used, was it pre-specified?	
Could the conduct or interpretation of the index test	"Yes" if a subset of index tests were conducted or interpreted in a different manner, or under different

have introduced bias?	conditions, or by people with differing levels of training "No" if it is clear that the conduct and interpretation of all index tests was appropriate and could not have introduced bias "Unclear if there is insufficient information presented to assess the potential of conduct and interpretation of the index test to introduce bias
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	"Yes" if the index test is not an RDT or if the test conduct or interpretation is not applicable to the review question "No" if there are no concerns based on the information presented
Reference Standard	
Is the reference standard likely to correctly classify the target condition?	"Yes" if the reference standard (culture or PCR) used in the paper matches those chosen in this protocol "Yes" if the culture or PCR is interpreted by appropriately trained/accredited individuals "No" if either of the above criteria are not met "Unclear" if insufficient information is presented
Were the reference standard results interpreted without knowledge of the results of the index test?	"Yes" if the paper states that the reference test is interpreted by individuals who did not have sight of the RDT result "No" if the result(s) of the RDT were known to the individual performing the reference test
Could the reference standard, its conduct, or its interpretation have introduced bias?	"Yes" if a subset of reference standard tests were conducted or interpreted in a different manner, or under different conditions, or by people with differing levels of training "No" if it is clear that the conduct and interpretation of all reference standard tests was appropriate and could not have introduced bias "Unclear if there is insufficient information presented to assess the potential of conduct and interpretation of the reference standard test to introduce bias
Are there concerns that the target condition as defined by the reference standard does not match the review question?	"Yes" if the target condition is not meningococcal, pneumococcal or H. influenzae meningitis or it is not clearly stated "No" if it is clearly stated that the target condition is meningococcal, pneumococcal or H. influenzae meningitis
Flow and timing	
Was there an appropriate interval between index test(s) and reference standard? (where recorded)	"Yes" if the time between RDT and reference standard was less than two weeks "No" if the time is longer than two weeks for a significant proportion of patients

	Note that this issue of timing does not affect treatment in this scenario (but it affects quality of sample rather than treatment)
Did all patients receive a reference standard?	"Yes" if all patients who received the index test also had the reference test "No" if not all the patients who received the index test also received the reference standard, or if a non-random sample was selected "Unclear" if this cannot be determined from the information presented in the paper
Did all patients receive the same reference standard?	"Yes" if the same reference standard was used for all patients "No" if different reference standards were used "Unclear" if this cannot be determined from the information presented in the paper
Were all patients included in the analysis?	"Yes" if there were no withdrawals or exclusions, or if those reasons are adequately explained with a flow chart "No" if withdrawals / exclusions are not explained or accounted for "Unclear" if withdrawals / exclusions cannot be determined or if there is insufficient information to judge this.
Could the patient flow have introduced bias?	"Yes" if subsets of patients or samples were treated, included or excluded in systematic ways which could have introduced bias. For example, if long periods of time between tests or inadequate sample transportation and storage arrangement may have influenced reference test reliability. "No" if patient flow is reported clearly and does not have the potential to introduce significant bias

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